

## STUDIES ON THE EFFECT OF PREGNANCY ON THE OVARY

H. SELYE, J. B. COLLIP, AND D. L. THOMSON  
*Department of Biochemistry, McGill University, Montreal*

### THREE FIGURES

While the effect of gonadotropic hormones on the maturation of follicles and the formation of corpora lutea has been studied by many workers, the influence of these hormones on the cells of the theca has received but little attention. This is probably due to the fact that the reactions of the theca are less conspicuous, and in part also to the greater interest of most investigators in the physiology of those cellular elements that are more directly concerned with reproduction. Thus, while the effect of removal of the hypophysis on the follicles and on the formation of corpora lutea is well known, the effect of this operation on the thecal cells has received little attention.

We have very recently reported(1) that the thecal cells undergo a marked transformation in hypophysectomized rats. The cytoplasm is very greatly reduced in volume, so that the nuclei come to lie close together. The outlines of the nuclei, formerly spindle-shaped, become circular; and the chromatin, which is normally more evenly distributed, agglomerates into larger granules which, as in the plasma cells, give to the nucleus the appearance of a wheel. The new cells thus formed, which undoubtedly arise by direct transformation of thecal cells or 'interstitial cells of the ovary' following the withdrawal of hypophyseal hormones, we propose to term thecal deficiency-cells.

Our previous experiments(1) show that these thecal deficiency-cells are very sensitive to the anterior-pituitary-

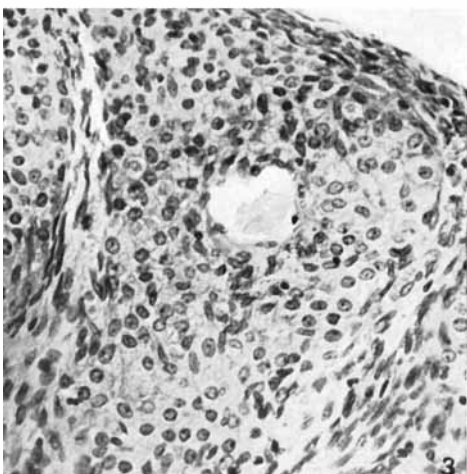
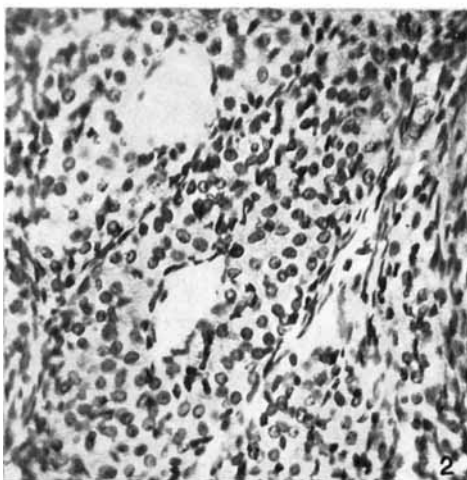
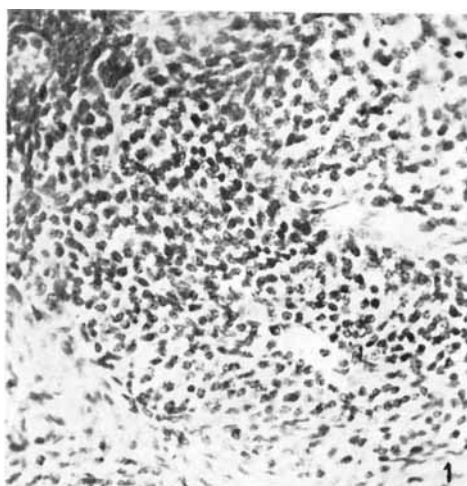
like hormone (A.P.L.) obtained from human pregnancy-urine, which readily causes them to change to a form closely resembling corpus luteum cells. This change, in fact, is the only obvious effect of this hormone on the ovary of hypophysectomized rats, whereas the gonadotropic hormone extracted from the anterior hypophysis itself can still produce maturation of follicles and formation of true corpora lutea by transformation of granulosa cells, restoring the ovary to an approximately normal condition(2). Thecal deficiency-cells are not found in the ovary if either of these hormones is present, and the occurrence of these cells indicates the absence of such substances.

In the rat, as in most other species, the corpora lutea of pregnancy are much larger than those of the normal cycle; they persist during the entire length of pregnancy, but rapidly undergo involution if gestation is interrupted. It is natural to ascribe the size and longevity of these corpora lutea to a change in the activity of the anterior hypophysis, which might be influenced by stimuli arising from the pregnant uterus. It has, in fact, been shown that in pregnant rabbits hypophysectomy promptly interrupts the endocrine activity of the corpora lutea(3). In contrast to this, however, it has been shown in the rat(4, 5) and mouse(6) that hypophysectomy at mid-pregnancy or later does not lead to abortion nor to premature involution of the corpora lutea; in fact, pregnancy may be prolonged. It thus appears that the corpora lutea of pregnancy are maintained, in these species, by some extra-hypophyseal influence. The corpora lutea of the normal oestrous cycle, on the other hand, are much smaller to start with, and although they do not rapidly disappear and may be

Fig. 1 Ovary of hypophysectomized rat. Numerous thecal deficiency-cells, showing grossly granular chromatin frequently assuming the typical wheel-like arrangement.

Fig. 2 Ovary of normal pregnant rat, showing accumulation of thecal cells. The nuclear chromatin is more evenly distributed. In many nuclei the nucleolus is easy to distinguish.

Fig. 3 Ovary of hypophysectomized rat treated with A.P.L. The thecal cells are very much like those shown in figure 2. They are, however, somewhat enlarged and show beginning luteinization.



recognized in the ovary for many months after hypophysectomy, they show histological signs of involution very soon after the operation. It is therefore tempting to suppose that in the pregnant rat or mouse the corpora lutea are actively maintained in structure and function by some influence not originating in the hypophysis. It seemed to us that, if this influence were a hormone comparable to the hypophyseal hormone or to A.P.L., it should not only maintain the corpora lutea, but also prevent the appearance of thecal deficiency-cells in the hypophysectomized pregnant rat.

Ten rats were accordingly hypophysectomized during the second half of gestation; all delivered normal litters. They were killed shortly after parturition, and the ovaries were examined histologically. The corpora lutea of pregnancy were indistinguishable from those of normal controls. The thecal cells, however, showed distinct signs of hormone-deficiency, especially in those cases in which the pituitary had been removed more than 4 days before parturition. Figure 1 shows an accumulation of thecal deficiency-cells around the vestiges of a dead ovum; the grossly granular nuclear chromatin, in which no nucleolus can be distinguished, frequently assumes the wheel-like arrangement seen in plasma cells or 'Radzellen.' The appearance of these nuclei is decidedly different from that of the nuclei of normal thecal cells, as shown in figure 2.

It seemed possible that luteinization of thecal deficiency-cells is in some way inhibited in the presence of pregnancy. Accordingly, ten more rats were hypophysectomized during the second half of gestation and treated with twenty units of A.P.L. daily. Four animals aborted after a few days of treatment; the rest delivered normally. All were killed at the end of pregnancy and examined as before. In no case did the ovaries contain thecal deficiency-cells; on the contrary, the thecal cells showed marked signs of luteinization (fig. 3). We are thus forced to conclude that whatever the influence is that maintains the structure and function of the corpora lutea of pregnancy in the rat—corpora quite different in size

and in histological appearance from those of the normal oestrous cycle or those produced by A.P.L. or pituitary extract—it is not a hormone comparable to the known gonadotropic hormones, since it fails to prevent the formation of thecal deficiency-cells after hypophysectomy. This result is in accordance with the well-known fact that it is not possible to demonstrate gonadotropic hormones in the placenta of rodents by the usual methods, and that administration of these hormones to experimental animals will never lead to corpora lutea of the type seen during gestation.

## SUMMARY

Both the gonadotropic hormone of the anterior pituitary and that obtained from the urine of pregnant women prevent the appearance of thecal deficiency-cells in the ovaries of hypophysectomized rats. Hypophysectomy during gestation does not alter the corpora lutea of pregnancy in any way, but does cause the thecal cells to show signs of hormone-deficiency. Hence the unknown influence which maintains the structure and function of the corpora lutea of pregnancy is not identical with either of the known gonadotropic hormones.

## LITERATURE CITED

- 1 SELYE, H., J. B. COLLIP, AND D. L. THOMSON 1933 On the effect of the anterior-pituitary-like hormone on the ovary of the hypophysectomized rat. *Endocrinology*, vol. 17, pp. 494-500.
- 2 COLLIP, J. B., H. SELYE, D. L. THOMSON AND J. E. WILLIAMSON 1933 Replacement of gonadotropic action of pituitary in the hypophysectomized rat. *Proc. Soc. Exp. Biol. Med.*, vol. 30, pp. 665-667.
- 3 FIROR, W. M. 1933 Hypophysectomy in pregnant rabbits. *Am. J. Physiol.*, vol. 104, pp. 204-215.
- 4 PENCHARZ, R. I., AND J. A. LONG 1933 Hypophysectomy in the pregnant rat. *Am. J. Anat.*, vol. 53, pp. 117-135.
- 5 SELYE, H., J. B. COLLIP, AND D. L. THOMSON 1933 Effect of hypophysectomy on pregnancy and lactation. *Proc. Soc. Exp. Biol. Med.*, vol. 30, pp. 589-590.
- 6 ——— 1933 Effect of hypophysectomy upon pregnancy and lactation in mice. *Proc. Soc. Exp. Biol. Med.*, vol. 31, pp. 82-83.